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(54) Title: OPTICAL RESOLUTION OF METHYLPHENIDATE BY 0,0'-BISAROYL TARTARIC ACIDS

(57) Abstract

Single isomer methylphenidate, selected from the *d-* and *l-threo*-enantiomers, has been obtained in purified form, to the extent of less than 2 % by weight of a contaminant selected from resolving agent and ritalinic acid. This is achieved by resolution of a mixture of enantiomers using an *0,0'*-diaroyltartaric acid as resolving agent.

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OPTICAL RESOLUTION OF METHYLPHENIDATE BY O,O'-BISAROYL TARTARIC ACIDS

Field of the Invention

This invention relates to the resolution of *threo* methylphenidate *via* crystallisation of diastereomeric salts, and to the especially pure enantiomers thus obtained.

Background of the Invention

Methylphenidate is a therapeutic agent that is widely used in the treatment of attention-deficient hyperactivity disorder. It is a controlled substance.

Methylphenidate was first prepared as a mixture of the *erythro* and *threo* racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereomer. It is now considered that it is the *d-threo* [or (*R,R*)] enantiomer that has the preferred therapeutic activity. Uses of this enantiomer are disclosed in PCT/GB96/01688, PCT/GB96/01689 and PCT/GB96/01690, the contents of which are incorporated herein by reference.

The resolution of *threo* methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, a process first reported by Patrick *et al* (The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987)), and subsequently used by other workers in the field (e.g. Aoyama *et al*, Journal of Chromatography, 494:420 (1989)). This is perceived to be a more efficient procedure than the method disclosed in US-A-2957880, wherein the corresponding amide of *erythro* methylphenidate (i.e. R-$CONR_2$ rather than R-CON_2Me) is resolved with tartaric acid prior to amide hydrolysis and equilibration at the benzylic centre, followed by esterification of the resultant *threo*-acid.

Summary of the Invention

This invention is based upon the discovery that racemic *threo* methylphenidate can be resolved using inexpensive carboxylic acids, specifically *O,O'*-diaroyltartaric acids, with surprising efficiency. In one embodiment of the present invention, either D- or L-*O,O*-di-toluoyltartaric acid forms diastereomeric salts with *threo*-methylphenidate, and these salts are very readily separated.

An important consequence of this discovery is that the desired enantiomer is obtained in greater chemical purity than by any prior method. Thus, while the process of Patrick *et al* may give the desired product contaminated with resolving agent, this contaminant can only be removed by repeated extractions that cause hydrolysis of the ester, leaving ritalinic acid as a contaminant.

Needless to say, a product intended for administration to humans should be as pure as possible. Surprisingly, the process of this invention gives the desired enantiomer in very high chemical and enantiomeric purity. In particular, the product is substantially free of resolving agent and/or ritalinic acid (and/or the opposite enantiomer). This purity can be at least 98%, preferably at least 99%, more preferably at least 99.5%, and most preferably at least 99.9%. The product may be in free base form or as a pharmaceutically-acceptable salt, e.g. the hydrochloride.

Description of the Invention

The process of this invention may be carried out under conditions that are generally known to those skilled in the art of classical salt resolution procedures. For example, a mixture of *threo*-methylphenidate and 1 molar equivalent of D-*O,O*-ditoluoyltartaric acid in an inert organic solvent is heated and then allowed to cool; the resultant precipitate is filtered, washed with an appropriate solvent and dried to afford directly a salt enriched in at least 97% ee *d-threo*-methylphenidate, i.e containing less than 1.5% of the opposite enantiomer. Enrichment to higher ee, e.g. at least 99%, can be simply achieved, by reslurrying in fresh solvent and filtering. This is a great improvement on the literature method using 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, described by Patrick *et al*, *supra*, in which the first crystallisation gave a salt corresponding to 85-90% ee material, and further recrystallisation of this material was necessary to raise the ee to 95-97%. The latter level of optical purity is achieved in the present invention in one crystallisation, with an overall higher yield. The method of this invention is therefore more efficient and more economical than the method described by Patrick *et al*.

Methylphenidate may initially be obtained as a salt of the resolving agent. This may be converted directly to the hydrochloride salt, or any other pharmaceutically-acceptable salt, by a salt exchange procedure. It may be preferable

to release the free base, by salt cracking. If desired, the free base can then be converted to a salt form. All these procedures are known to those skilled in the art.

Further advantages of the present invention are as follows:

(i) Salt cracking at pH 9-10 is by addition of aqueous sodium hydroxide, whereas dilute aqueous sodium carbonate is needed for salts of the more base-labile 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate; this renders the novel process more volume efficient.

(ii) Lower volume of aqueous medium in (i) means fewer extractions into organic solvent (TBME rather than diethyl ether) to isolate methylphenidate free base.

(iii) Chemical robustness of DTTA allows for clean and efficient recovery.

Either isomer of methylphenidate can be easily obtained by this procedure, e.g. by simply using the D- or L-isomer of the diaroyl tartaric acid derivative as required.

Single isomer methylphenidate according to this invention, especially pure *d-threo*-methylphenidate, can be used in therapy for the same purposes as the racemate, e.g. in the treatment of ADHD or narcolepsy. The compound can be formulated with any suitable carrier, in any suitable dosage, as will be apparent to one of ordinary skill in the art. Reference in this context may be made to any of the three PCT Applications identified above.

The following Example illustrates the invention.

Example

Ditoluoyl-D-tartaric acid (5.033 g, 12.4 mmol) was suspended in a solution of 2% methanol in acetone (10 ml), and a solution of *threo*-methylphenidate (2.9 g, 12.4 mmol) in the same solvent (10 ml) was added. The solution was gently warmed to reflux whereupon all the reagents dissolved. The solution was immediately cooled and crystals began to form. The solution was allowed to stand at 4°C for 17 hours and was then filtered. The crystals were washed with acetone (3 x 15 ml) and dried *in vacuo* to yield the ditoluoyl-D-tartrate salt of *d-threo* methylphenidate (3.516 g, 44.3% by weight; corresponding to 97% ee *d-threo* methylphenidate, as determined by chiral HPLC after salt cracking). The mother

liquors were dried *in vacuo* to yield the ditoluoyl-D-tartrate salt of *l-threo*-methylphenidate as a solid, dry form (4.508 g, 50.5% yield, 88% ee).

The ditoluoyl-D-tartrate salt of *d-threo*-methylphenidate (3.486 g), obtained as described above, was suspended in 2% methanol in acetone, and warmed to c. 40°C and cooled. This did not dissolve the solid which was stirred at room temperature for 24 hours. The suspension was filtered, the solid washed with acetone (10 ml) and dried *in vacuo*, to yield diastereomerically pure material (3.209 g, 92% recovery, corresponding to >99% ee *d-threo*-methylphenidate).

Repeating this protocol using isopropanol: methanol as the solvent, gave the same salt, on initial crystallisation, enriched in at least 98%. Reslurrying increased this.

For the purposes of comparison, USP grade *dl-threo*-methylphenidate hydrochloride (3.36 g) was dissolved in an aqueous solution of sodium carbonate (45 ml, 2% w/v), and the clear solution was extracted with diethyl ether (3 x 50 ml). The combined ethereal layers were dried ($MgSO_4$), filtered, and evaporated to dryness. The resulting pale yellow oil together with (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (3.36 g) were dissolved in a hot mixture of acetone/methanol (95:5). The solution was gently stirred and cooled to 5°C and maintained for 12 hours. The resulting white crystals (2.98 g) were isolated by filtration and recrystallised from acetone/methanol (98:2). This product was then treated with a 2% aqueous solution of sodium carbonate and extracted with diethyl ether (4 x 50 ml). The combined ethereal layers were dried ($MgSO_4$) and filtered. An excess saturated solution of hydrogen chloride in ether was then added and the resulting hydrochloride salt was filtered, rinsed with ether, and recrystallised from methanol/ether. The resulting white crystalline product was analysed by HPLC and proton NMR:

% w/w *l-threo*:3.7%

e.e.:92.6%

ritalinic acid:trace amount but not quantified by HPLC or NMR

resolving agent:approximately 4% by NMR

CLAIMS

1. Single isomer methylphenidate, selected from the *d*- and *l-threo*-enantiomers, or a pharmaceutically-acceptable salt thereof, in combination with less than 2% by weight of a contaminant selected from resolving agent and ritalinic acid.

2. Methylphenidate according to claim 1, in combination with less than 1% by weight of the contaminant.

3. Methylphenidate according to claim 1, in combination with less than 0.5% by weight of the contaminant.

4. Methylphenidate according to claim 1, in combination with less than 0.1% by weight of the contaminant.

5. Single isomer methylphenidate, selected from the *d*- and *l-threo*-enantiomers, or a pharmaceutically-acceptable salt thereof, which is at least 98% pure.

6. Methylphenidate according to claim 4, which is at least 99% pure.

7. Methylphenidate according to claim 4, which is at least 99.5% pure.

8. Methylphenidate according to claim 4, which is at least 99.9% pure.

9. Methylphenidate according to any preceding claim, as the free base.

10. Methylphenidate according to any of claims 1 to 8, as the hydrochloride.

11. A pharmaceutical composition comprising *d-threo*-methylphenidate according to any preceding claim, and a pharmaceutically-acceptable diluent or carrier.

12. Use of *d-threo*-methylphenidate according to any of claims 1 to 10, for the manufacture of a medicament for use in the treatment of a condition susceptible to treatment with methylphenidate.

13. Use according to claim 12, wherein the condition is attention-deficient hyperactivity disorder or narcolepsy.

14. A process for preparing substantially single enantiomer *d*- or *l-threo*-methylphenidate, which comprises resolution of a mixture of enantiomers using an *O,O'*-diaroyltartaric acid as resolving agent.

15. A process according to claim 14, wherein the resolving agent is D- or L-*O,O*-ditoluoyltartaric acid.

16. A process according to claim 14 or claim 15, which additionally comprises salt cracking using aqueous alkali metal hydroxide.

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/GB 97/00185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 957 880 A (R. ROMETSCH) 25 October 1960 cited in the application see the whole document see column 6, line 11 - line 29 ---	1-13
X	J. MED. CHEM. (1996), 39(6), 1201-9 CODEN: JMCMAR;ISSN: 0022-2623, 1996, XP000602079 DEUTSCH, HOWARD M. ET AL: "Synthesis and pharmacology of potential cocaine antagonists. 2. Structure-activity relationship studies of aromatic ring-substituted methylphenidate analogs" see the whole document scheme 1, table 1 --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 1997	12.03.97
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. PHARMACOL. EXP. THER. (1987), 241(1), 152-8 CODEN: JPETAB;ISSN: 0022-3565, 1987, XP000602457 PATRICK, KENNERLY S. ET AL: "Pharmacology of the enantiomers of threo-methylphenidate" cited in the application see the whole document	1-13
Y	WO 95 31436 A (MERRELL DOW PHARMA ;NAKAMURA MITSUO (JP); SHIGA MASATOSHI (JP)) 23 November 1995 scheme B, page 4	14-16
X	J. PHARM. SCI. (1967), 56(12), 1689-90 CODEN: JPMSAE, 1967, XP000602090 SHAFI'EE, ABBAS ET AL: "Absolute configurations of enantiomeric pheniramines, methylphenidates, and pipradrols" see the whole document	1-13
Y	PATENT ABSTRACTS OF JAPAN vol. 95, no. 009 & JP 07 247286 A (SANKYO CO LTD), 26 September 1995, see abstract	14-16
X	J. LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, vol. XXXIV, no. 10, 1994, pages 989-997, XP000602493 see the whole document	1-13

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Information on patent family members

Inten .nal Application No
PCT/GB 97/00185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2957880 A	25-10-60	NONE	
WO 9531436 A	23-11-95	AU 2284095 A	05-12-95
		CA 2189000 A	23-11-95
		ZA 9503793 A	19-01-96